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REVIEW ARTICLE

Immunological resilience and biodiversity for prevention of allergic diseases and asthma

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Abstract

Increase of allergic conditions has occurred at the same pace with the *Great Acceleration*, which stands for the rapid growth rate of human activities upon earth from 1950s. Changes of environment and lifestyle along with escalating urbanization are acknowledged as the main underlying causes. Secondary (tertiary) prevention for better disease control has advanced considerably with innovations for oral immunotherapy and effective treatment of inflammation with corticosteroids, calcineurin inhibitors, and biological medications. Patients are less disabled than before. However, primary prevention has remained a dilemma. Factors predicting allergy and asthma risk have proven complex: Risk factors increase the risk, while protective factors counteract them. Interaction of human body with environmental biodiversity with micro-organisms and biogenic compounds as well as the central role of epigenetic adaptation in immune homeostasis have given new insight. Allergic diseases are good indicators of the twisted relation to environment. In various non-communicable diseases, the protective mode of the immune system indicates low-grade inflammation without apparent cause. Giving microbes, pro- and prebiotics, has shown some promise in prevention and treatment. The real-world public health programme in Finland (2008–2018) emphasized nature relatedness and protective factors for immunological resilience, instead of avoidance. The nationwide action mitigated the allergy burden, but in the lack of controls, primary preventive effect remains to be proven. The first results of controlled biodiversity interventions are promising. In the fast urbanizing world, new approaches are called for allergy prevention, which also has a major cost saving potential.

KEYWORDS

allergy prevention, allergy program, biodiversity, immunological resilience, microbiome

1 | INTRODUCTION

From 1950s, the *Great Acceleration* of human activity coincides with the *Anthropocene*, a title suggested for a geological epoch of human impact on earth's ecosystems.[1] Health and life expectancy have improved in high income countries but much at the expense of environment. Population explosion, escalating urbanization, and overuse of natural resources have become the rule. The increase in emissions of greenhouse gases, global warming, massive extinction of species, and pollution are all part of the Anthropocene. We might be loosing resilience as individuals and communities and face epidemics of both communicable (fast) and non-communicable (slow) diseases, with unpredictable outcomes.

Dawn of non-communicable diseases was evident in 1960s, when also increase of allergic diseases and asthma became obvious in most developed countries. Indeed, they are good indicators of the modern health hazards, for example, shown in the Finnish and Russian Karelia.[2] In a relatively short period of time, after the second world war, two geoclimatically and genetically close populations have developed contrasting immunological expression. In Russian Karelia, hay fever was rare, food allergies few and peanut allergy unknown. The contrast is neither explained by hereditary factors nor by air pollution or common chemicals but rather by changes in lifestyle and environment. Understanding the underlying reasons of this disparity would enable measures for prevention. Allergy is not an isolated case but concurrent with the increase of both type I and II diabetes, cardiovascular diseases, obesity, inflammatory bowel diseases, even mental disorders and cancer.[3]

Resilience is defined as an ability to recover from or adjust to change or misfortune (Merriam-Webster Dictionary). Resilience is multidimensional; immunological, psychological, and societal aspects are all critical. Lack of it may be the main reason for the increasing burden of non-communicable diseases. Lack of the resilient immunity at individual or community level is also obvious during the current COVID-19 pandemic. In general, resilience of the immune system means having the capacity to adapt to challenges by establishing, maintaining, and regulating an appropriate immune response. A resilient immune response is a healthy state: not too passive, not too active, and able to return to homeostasis. It is a fine balance between useful and harmful response, and no response at all. If resilience is lost, disease may follow.

Microbe-immune system interplay is decisive for resilience and the immune homeostasis. If the crosstalk is not versatile enough, dysregulation arises. Reduced contact to environmental microbial diversity is probably the main reason of the compromised immunological resilience of populations living in the modern, urban environment.[4,5] In logistic regression models, risk factors of the disease in question are evaluated, but the models seldom identify protective factors as explanations or confounders[6] (Figure 1).

In this paper, we present some of the recent insights of immunological resilience and biodiversity supporting health and preventing allergic diseases.

Future research perspectives

- Knowledge of the determinants of immunological resilience is a prerequisite for primary prevention.
- Controlled and real-world interventions to study both mechanisms and clinical effect of biodiversity.
- Functional capacity of the microbiome, what are the decisive factors: richness, diversity, or composition?
- Transfer of microbiota from the environment to human body.
- Interaction of epigenetic markers with human or environmental microbiota.
- Validation of the cellular effects of biogenic (volatile, organic) compounds in clinical setting.

Milestones

- Recognition of human body as a community of species (holobiont) and genomes (hologenome).
- Insight of epigenetic regulation of immune adaptation under continuous environmental pressure.
- Biodiversity hypothesis of health. Recognition biodiversity as a major determinant of human health (WHO, The Convention on Biological Diversity 2015).
- Evidence-based nature/biodiversity loss, verified by a long-term follow-up (WWF, Living Planet Index 1970–2020).
- Concept of Planetary Health as the health of human civilization and the state of natural systems (The Rockefeller Foundation-Lancet Commission 2015).
- Paradigm shift in allergy prevention, from avoidance to immunological tolerance/resilience. Implementation of the first national programme for prevention (The Finnish Allergy Programme 2008–2018)

2 | DIVERSITY OF LIFE

Biological diversity comes in two flavors. *Structural* biodiversity consists of layers of life, starting from the diversity of ecosystems followed by numerous species living within, and reaching the complex genetic and phenotypic variation between individuals. Biodiversity is also *functional*, indicating complex interactions between species and their biotic and abiotic environment. Microbial diversity has two dimensions, *alpha* and *beta diversity*. In any given sample, *alpha diversity* is a measurement of species richness (number of different taxa) and evenness (abundance of the taxa in question). *Beta diversity* a distance measure between samples and represents the compositional dissimilarity or heterogeneity. Defining and measuring biodiversity accurately is, however, under constant debate.

In early 2021, the Global Biodiversity Information Facility, a database collecting global species occurrence, listed 2,725,553 species

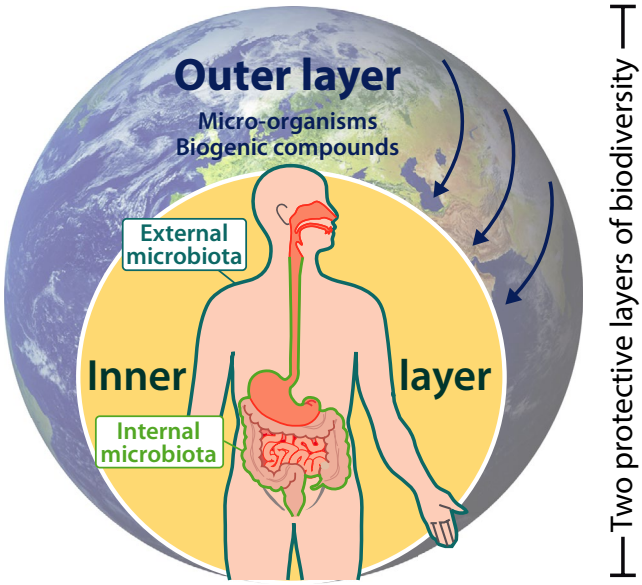

FIGURE 1 Human body is protected by two nested layers of biodiversity. They consist of micro-organisms residing in the living environment and on the external and internal surfaces of the body. The inner layer is dependent on the microbial colonization from the outer layer, from air, soil, and natural waters. In natural environment, humans also breathe biogenic (volatile, organic) compounds with protective cellular functions,[6] (modified)

in 8 kingdoms of life (gbif.org). The majority of the species are still undescribed or not included to this database. Moreover, those kingdoms or domains representing the biodiversity that is invisible to human eyes, such as in bacteria, archaea, and microscopic fungi, do not have a clear definition of species. While most unknown species belong to these kingdoms, for example, insects are also poorly described. The total number of eukaryotic species, that is, other kingdoms than bacteria, archaea, and viruses, vary somewhere between 5 and 8.7 million.[7,8] However, when accounting all forms of life, estimates can reach up to 1 trillion species.[9]

2.1 | Environmental microbial exposure

2.1.1 | Urban vs. rural exposure

Microbial exposure and its diversity depend on the environment and living habits.[10] Urban, man-made surface soil materials have poorer microbial communities compared to forest soil.[11] Consequently, microbial communities on skin and in airways of children and adults tend to be poorer and more homogenous in urban than in rural individuals.[4,12,13] This is also evident even in newborns and pets.[14-16] This parallels with overall poverty of both macroscopic and microscopic urban biodiversity (Figure 2).

Within a city, the green areas have a considerable impact on microbial diversity.[17] Macroscopic diversity influences the diversity of microbial communities; species-poor grass fields hold less microbes than species-rich forested areas both in soil and air.[18,19] Importantly, revegetation enriches soil microbial communities indicating that urban green spaces can facilitate beneficial microbial exposure.[20] Pollutants may shape plant and microbial communities[21-23] and are associated with negative functional potential of gut microbiota.[24-26] Thus, exposure to beneficial environmental microbiota can be improved by increasing vegetation and reducing pollution.

2.1.2 | Indoor microbiota

In urban settings, the indoor microbial environment is largely composed by human skin microbiota.[27] People are exposed to their own microbes. Indoor microbial composition differs between rural and urban areas,[28-30] and between homes practicing farming or not.[10,31] When dirt was collected from doormats, urban dwellers carried indoors less microbiota than their rural counterparts.[28] In urban areas, the summertime biodiversity of doormat dirt was at the same level as the wintertime minimum in rural areas.[32] The high coverage of built environment around homes reduced the diversity of environmental microbiota carried indoors, but already a backyard rich of plants can make a difference for individual microbiota.[28,33]

Lifestyle factors have a stronger effect on human microbiome than genetics as shown by studying identical twins.[34] While microbial communities differ between Western and indigenous populations such as tribes and hunter-gatherers,[35] immigration, for example, from Thailand to United States causes a rather immediate westernization of gut microbiota.[36] The analyses of microbiota differences between populations are confounded by a number of factors. Therefore, studying people in the same country but with contrasting lifestyles or environments is likely to give most relevant information.[37]

2.2 | Biodiversity in health and disease

2.2.1 | Human body as an ecosystem

Lynn Margulis used the concept *Holobiont* to describe the host (animal or plant) of being a community of species subject to continuous evolutionary pressure.[38,39] Holobiont species are *bionts*, and *hologenome* is the combined genome of the bionts. The concept binds human health tightly with homeostasis of the holobiont (Figure 3).

Natural environment supports human health in a holistic manner. Both visiting natural areas and living in green surroundings associates with physical, mental, and social health. Moreover, a natural living environment associates with reduced risk of mortality to any causes,[40] also in urban areas.[41]

2.2.2 | Infectious diseases

A meta-analysis showed that biodiversity reduced the prevalence of diseases caused either by micro- or macroparasites, consistently in

FIGURE 2 Urban, build environment, and changes in lifestyle (left) have increasingly disconnected children from the natural air, soil, and waters, the evolutionary home of *Homo sapiens* (right). Photos: M. Andersson, J. Haahtela, with permission

plants, wildlife, and humans.[42,43] Especially vector-borne, generalist wildlife, and zoonotic pathogens are affected by changes to biodiversity.[44] Interestingly, while diversity of parasites is also declining along other biodiversity,[45] the risk of zoonoses increases. This may be due to the hampering of ecological mechanisms controlling pest abundance as well as the increased human contact with wildlife.

As biodiversity is lost from ecosystems, the persisting species tend to be those most likely to harbor and transmit pathogens; abundant, widespread, and resilient.[43] Therefore, changing species composition, rather than diversity per se, can affect disease risk.[44] Moreover, even though the individual pathogen load may not change, the risk for an infection is higher in environments with low biodiversity.[42,43,46] However, for some infectious diseases, measures to improve hygiene, increasing wealth, and targeted biomedical management can be more effective for disease prevention than biodiversity conservation.[44,47]

2.2.3 | Non-communicable diseases

Biodiversity tends to support well-being and reduce the risk of asthma and allergic diseases.[4,48] Visiting green environments has been associated with reduced stress and blood pressure.[49] Environmental diversity was associated with reduced risk of asthma in children,[50] and increasing landscape-level biodiversity with reduced public hospital admissions due to respiratory diseases.[51]

All green is not, however, equal in terms of health outcomes. Living next to grassy areas or to coniferous forests has been associated even with an increased risk of asthma in urban children, possibly due to airborne biotic and abiotic contaminants.[48,52] Even living some hundred meters from a green space does not guarantee exposure to rich environmental microbiota.[53,54] Nevertheless, diverse vegetation in the immediate surroundings of homes, urban daycares, and schools have associated with reduced allergic sensitization[4] and improved lung function[55] suggesting that immediate exposure is of importance.

3 | EPIGENETIC PLASTICITY FOR IMMUNOLOGICAL RESILIENCE

Individuals with specific genotypes have different responses to the same exposure.[56] This so-called flip-flop pattern results in poor replicability of associations between genotypes and disease, if environmental exposure is not considered. Epigenetic modifications are emerging as promising mechanisms to understand the plasticity of gene-environment interaction.

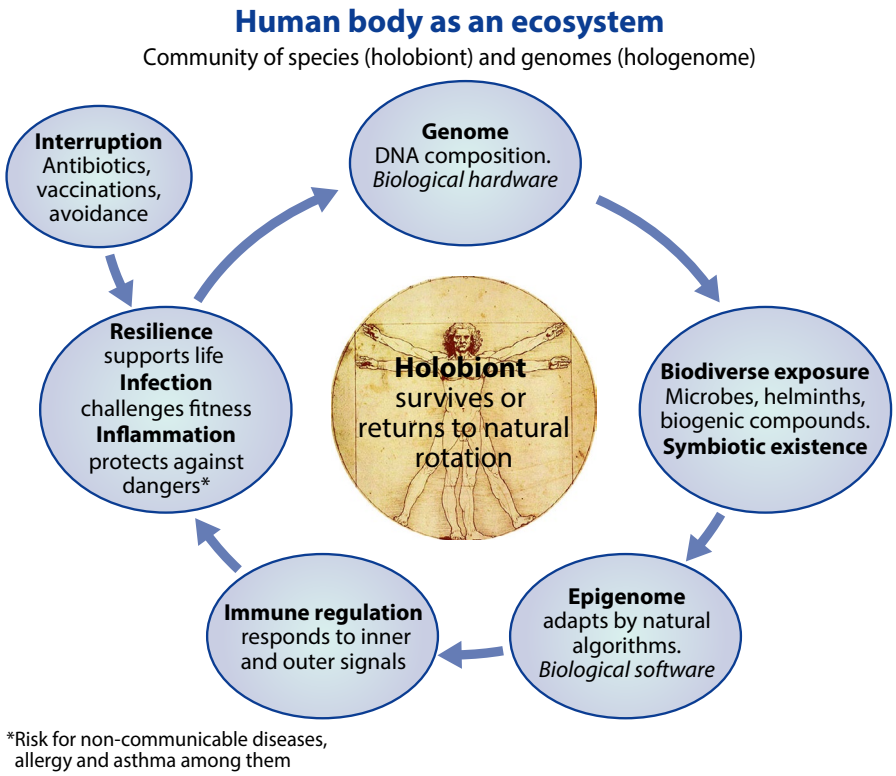

FIGURE 3 Human body as a community of species and genomes. Biotically diverse exposure calls for epigenetic signaling to modify and adapt immune regulation for resilience. Interruption may degrade or improve resilience. [In the middle, the drawing *Vitruvian Man* by Leonardo da Vinci, from the end of 15th century. Human body is an expression of the microcosm connected to the macrocosm]

Epigenetics refers to mechanisms that perpetuate alternative gene activity in the context of the same DNA sequence.[57] Epigenetic modifications predispose health or disease by determining regions of the genome accessible to the transcription machinery. Resilience of the immune system depends on epigenetic adaptation throughout life. DNA methylation, histone modifications, and small and long non-coding RNAs (lncRNAs) are hot topics in research.[58] They play a central role in mediating environmental effects on health and disease (Figure 4).

3.1 | Epigenome-wide studies (EWAS)

A genome-wide DNA methylation study of childhood asthma, including age-matched controls, found 14 asthma associated CpG sites in whole blood which were replicable in independent study cohorts.[59] Altered DNA methylation profiles were found in eosinophils and cytotoxic T cells. Most of the modified CpG sites were identified at the age of 8 years, but none at birth emphasizing the postnatal environmental exposure in allergic disease.

Genome-wide DNA profiles have been investigated also in nasal epithelial samples.[60-62] In the PIAMA birth cohort, the EWAS analysis identified replicable DNA methylation profiles associated with asthma, rhinitis, and sensitization to aeroallergens.[60] Cardenas et al[61] reported that the differentially methylated regions in nasal epithelium associated with allergic asthma, Th2 signaling, eosinophilia, and airway epithelial defense. Both studies concluded that the nasal epigenome may serve as a biomarker for asthma, rhinitis and airway inflammation.

3.2 | Long non-coding RNAs

lncRNAs are an example of a rather new class of regulatory RNAs transcribed from DNA, but typically not translated into proteins.[57] lncRNAs are involved in both immune cell development and function.[63-66] Transcriptomics analyses of the Karelian Allergy cohort revealed depressed innate immunity signaling in Russian subjects compared with their Finnish counterparts.[2] Moreover, the gene-microbe network was richer and more diverse in the Russian subjects. Interestingly, a large part of the up-regulated genes in the Russian subjects were represented by lncRNAs, while one third of the down-regulated genes were immune-related. Indeed, lncRNAs may control host immune responses during microbial infection and Th2 differentiation.[63,64,66] Differentially expressed lncRNAs may operate as mediators of both gene-environment and gene-microbe interaction, regulating responses not only against microbes but also against foreign proteins released, for example, by pollens.[2]

3.3 | Interaction with microbiota

Epigenetic markers may distinguish patient groups, but little is known of their interaction with environmental or human microbiota, or with the immune system in general.[67] Bacterial products such as peptidoglycans and short chain fatty acids (SCFAs) alter hematopoiesis by increasing neutrophils, macrophages, and dendritic cells.[68] They modify immune reactivity of both myeloid[69] and epithelial[70] cells, potentially through epigenetic reprogramming. A high-fiber diet[71] or exposure to a biodiverse living environment, including

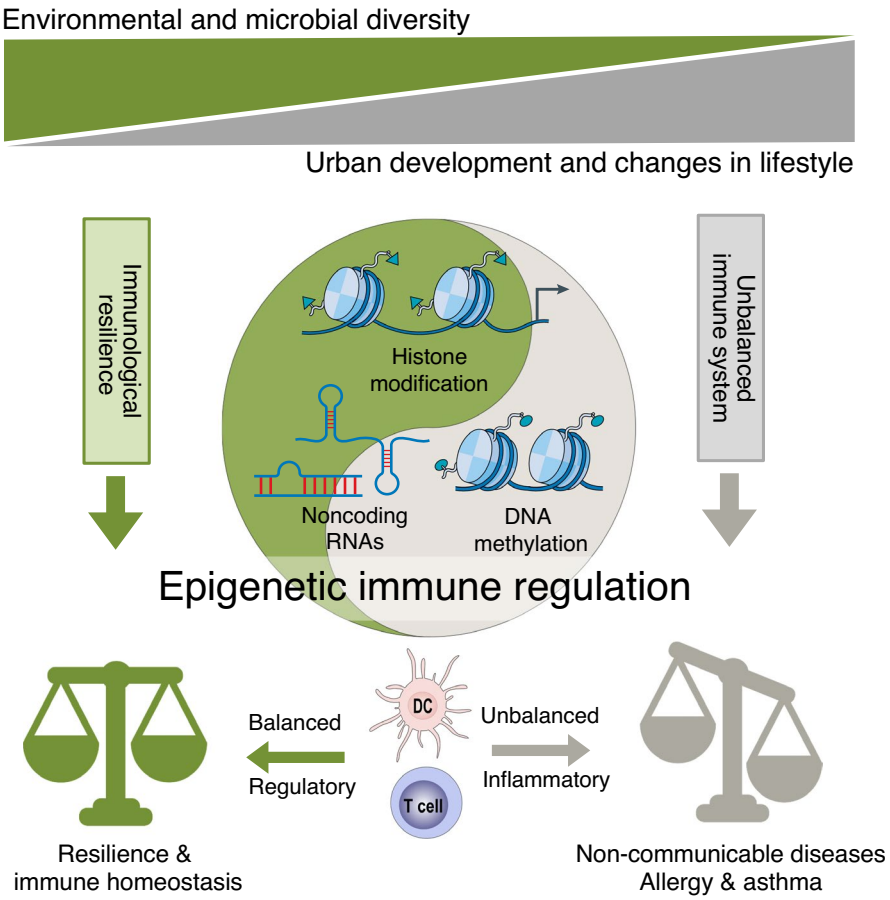

FIGURE 4 Epigenetic immune regulation is under a lifetime pressure of complex environmental factors, also called the exposome

soil exposure,[72] promotes the outgrowth of intestinal bacteria. For example, members of the *Bacteroidetes* phylum generate from dietary fibers epigenetically active, immunomodulatory SCFAs, which inhibit histone modifications.[71,73] This leads to hyperacetylation of intestinal macrophages and to the differentiation of Th1/Th17 effector T cells or Treg cells.

In mice on a high-fiber diet, SCFAs enhanced generation of dendritic cells, with an impaired ability to activate Th2 effector cells, thus protecting against allergic airway inflammation.[71] *Clostridia* species able to generate SCFAs, associate with the resolution of food allergies.[74] These microbes also induce colonic Treg cells through histone H3 acetylation and protect against sensitization to food allergens.[75]

Acinetobacter lwoffii induces immune tolerance in both humans and animal models by activating Th1 and Treg differentiation, probably by epigenetic modifications.[76] In support of this, Brand and coworkers demonstrated that prenatal administration of *A. lwoffii* prevented asthmatic phenotype in the progeny mediated by changes in H4 acetylation of IL4 and IFNg promoter regions.[77]

The gut microbiome produces diverse neuroendocrine molecules acting as modulators on *gut-brain*, *gut-skin*, or *gut-lung* interaction, in which epigenetic mechanisms like histone modifications and DNA methylation are involved. For example, gut microbiota may influence on cognition and Alzheimer disease through regulation of neural, endocrine, and immune pathways.[78] One detail is skin itch, which is inhibited γ-aminobutyric acid (GABA) produced by gut *Lactobacillus* and *Bifidobacterium* species.[79]

Taken together, these results suggest that interventions which include epigenetically active microbes or microbial metabolites are useful both for primary and secondary allergy prevention.

The functionally most important epigenetic mechanisms are presented in Table 1.

4 | CONTROLLED AND OPEN INTERVENTIONS

Direct, regular contact with soil or plants diversifies human microbiota,[81] observed both on the skin[82] and in the gut.[33] For example, children, in similar daycares, who spend several hours a day in natural environment, have more diverse skin microbiota than children with less outdoor activities. However, it is possible that environmental microbes are only transient members of the human microbiota,[83] indicating that frequent contact with environmental microbes may be needed for immuno-regulatory effects to arise.

4.1 | Biodiversity interventions

There is an urgent need to test various exposure strategies, ranging from active gardening and outdoor activities to indoor and personalized interventions. A key question is whether we should be

TABLE 1 Epigenetic mechanisms and their proposed functions. The data are mostly based on the review of Q. Zhang and X. Cao[80]

Epigenetic mechanism	Function
DNA methylation and oxidation	• DNA methylation of CpG dinucleotides is associated with transcription silencing. • Methyl-CpG oxidation mediates active DNA demethylation or other functions.
Histone modification • Acetylation • Methylation • Phosphorylation	• Various roles in transcription regulation.
Nucleosome remodeling	• Chromatin changes control DNA accessibility and thus the binding of transcription regulators, transcription factors and transcription co-activators.
Non-coding RNAs (ncRNAs) • Long non-coding RNAs (lncRNAs) • Competing endogenous RNAs (ceRNAs) • Enhancer RNAs (eRNAs) • Circular RNAs (circRNAs) • microRNAs (miRNAs)	• Divergent roles in cellular responses via RNA–DNA, RNA–RNA and RNA–protein interactions.
RNA modification and "epitranscriptome"	• Functional modifications in mRNAs and ncRNAs constitute the "epitranscriptome" representing a new layer of epigenetic regulation at the RNA level. • The regulatory roles of RNA modifiers in innate immunity and inflammation are still poorly understood.

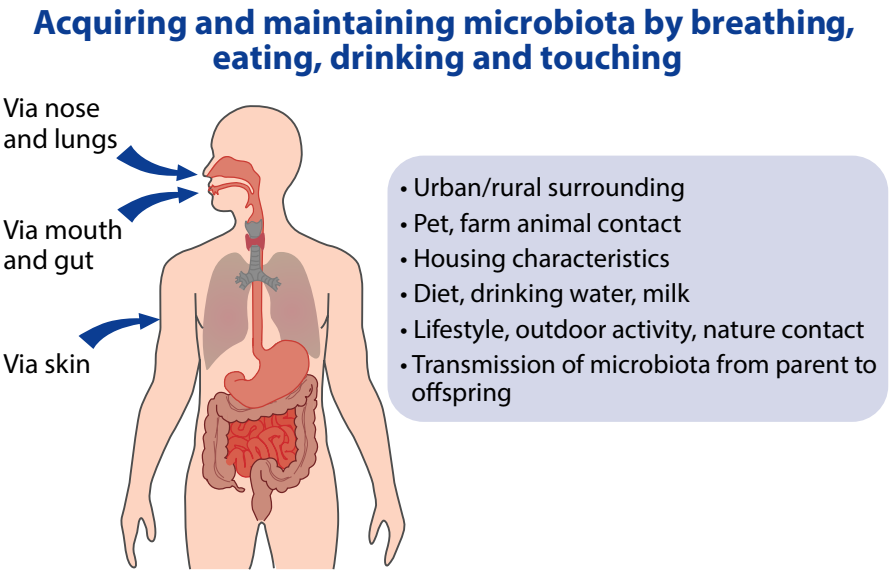

FIGURE 5 We connect to the environment with senses and activities, and host, what we breathe, eat, drink, and touch. Activities in biotically diverse environment together with unprocessed food provide human body with microbiota for immune regulation,[84] (modified)

exposed to microbes by ingesting, inhaling, being in skin contact, or by all these means to promote balanced immune homeostasis,[84] (Figure 5).

Interventions can modify the living environment, change the living habits, or target for both. Studies that enhance nature contacts and follow changes in the commensal microbiota and immune regulation are ongoing, but results have not been published.[85] Urban citizens want the potential benefits of environmental microbial biodiversity, providing that the efficacy and safety of the nature-based solutions have been shown.[86-88]

Composition of the microbial communities and their dynamics of transfer in the introduced biodiversity elements are poorly known. When urban volunteers rubbed their hands in gardening soils materials for 20 s and washed hands in tap water, they attained markedly higher microbial diversity on the skin.[89] In a 2-week intervention, volunteers exposed themselves to a soil-like material, rich of microbes, or just continued life as usual.[90] The exposure increased the microbial diversity of both skin and stool. The change was associated with the expression of TGF-beta by peripheral blood mononuclear cells.

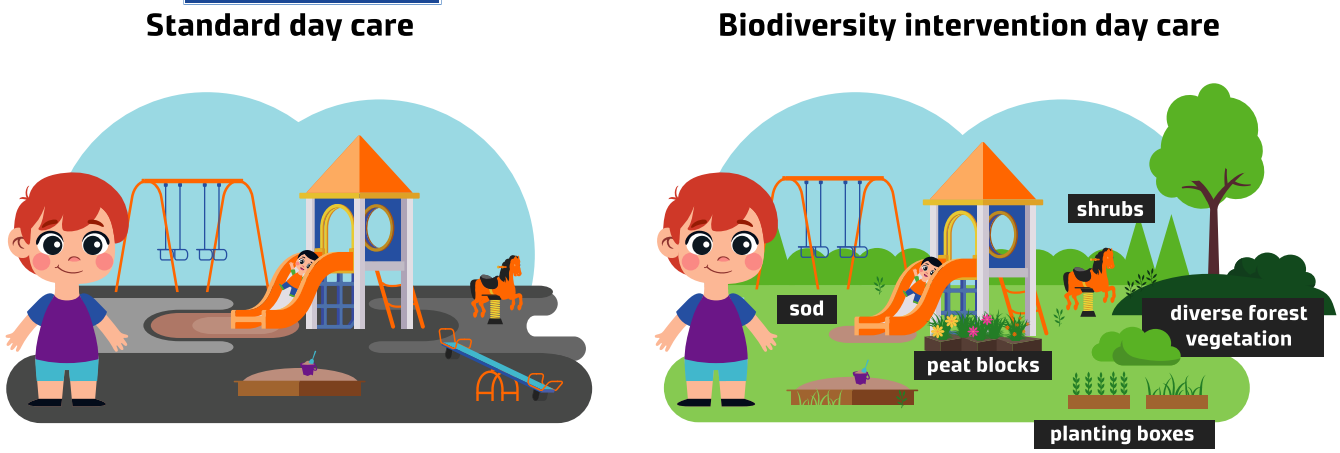

FIGURE 6 In the biodiversity intervention, the daycare yards were enriched with vegetated boreal forest soil blocks, sod, peat blocks, and by gardening the soil for growing vegetables[91]

TABLE 2 Practical advice to improve immunological resilience and treatment in the Finnish Allergy Programme (2008–2018)[97]

Primary prevention	Secondary (tertiary) prevention

• Support breastfeeding, solid foods from 4 to 6 months
• Do not avoid environmental exposure unnecessarily (eg, foods, pets)
• Strengthen immunity by increasing connection to natural environment
• Strengthen immunity by regular physical exercise
• Strengthen immunity by healthy diet (eg, traditional Mediterranean or Baltic type)
• Use antibiotics with care. Majority of microbes are useful and support health
• Probiotic bacteria in fermented food or other preparations may strengthen immunity
• Do not smoke
	• Promote regular physical exercise, especially in asthmatics
	• Promote healthy diet (Mediterranean or Baltic type of diet improves asthma control)
	• Consider use of fermented food or other preparations, including probiotic bacteria
	• Consider allergen specific immunotherapy:
	  • Allergens as is (foods)
	  • Sublingual tablets or drops (eg, grass pollen, birch pollen, house dust mite)
	  • Subcutaneous injections
	• Hit early and hit hard respiratory/skin inflammation; find maintenance treatment for long-term control
	• Do not smoke.

4.2 | Enriching daycare yards

Roslund et al[91]enriched daycare yards with vegetated boreal forest soil blocks, sod, peat blocks, and gardening soil for growing vegetables (Figure 6). The study had two control arms, one without biodiversity intervention and one with nature-oriented daycare. Within 1 month, the diversity of skin microbiota as well as the abundance of *Proteobacteria* were increased in children attending the intervention daycare compared to children in the non-modified daycare. The increased ratio between serum interleukins 10 and 17A indicated activation of immune regulatory pathways. Importantly, the increase of immunomodulatory cytokines and regulatory T cells was associated with a higher diversity of the skin *Gammaproteobacteria*.

5 | THE FINNISH NATIONWIDE ACTION FOR PREVENTION

In Finland (population ca. 5.5 million), several successful national public health programmes have been completed to control respiratory diseases.[92]The Asthma programme (1994–2004) improved the management by treating asthma primarily as an inflammatory disease.[93] For allergic conditions, there are no reports of coordinated action plans to mitigate the burden nationwide. The recent Allergy Programme (2008–2018) was taken to emphasize prevention, tolerance, and nature relatedness[94,95] (Table 2). The main aim was to transform the strategy from avoidance to tolerance/resilience and focus on allergy health, especially in children.[96] Severe clinical manifestations were given special attention. A major educational effort both for healthcare professionals and lay public followed.

Indeed, revisiting the allergy paradigm and systematic education mitigated the burden of allergic diseases in the Finnish society.[97,98] As this real-world intervention lacked controls, the true impact of primary prevention remains to be verified. The Finnish experience is, nevertheless, different from the global trend of asthma and allergy, the burden of which has remained high or is even increasing.[99-101] This indicates that the current prevention strategies are ineffective and new approaches are required.

5.1 | Case food allergy

In the Finnish Allergy Programme, food allergy guidance and practices were changed with favorable results.[102,103] The thinking was

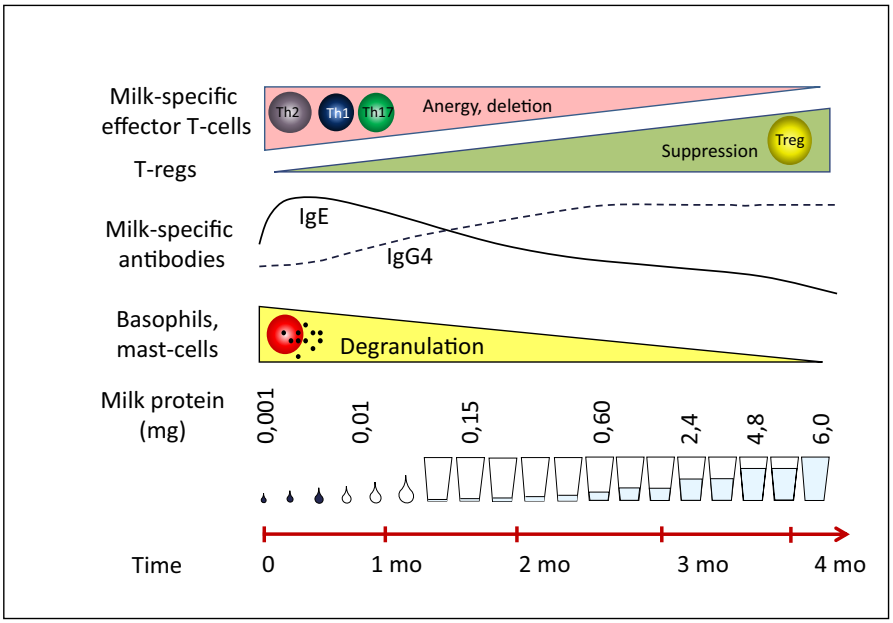

FIGURE 7 The immunological changes during the oral immunotherapy (OIT)

based on new knowledge of immunological tolerance. The diversity of foods given at 6 months of age seems to protect from development of food allergies.[104,105] Most societies have adapted recommending use of solid foods at 4–6 months of age. There is likely an effect of this on the gut microbiome, but more data are required. Interestingly, a recent study indicated that oral immunotherapy (OIT) in peanut allergic adults increased gut microbial diversity.[106] Thus, the gut microbiota seems to shape the host immune system and vice versa.

Dual allergen exposure hypothesis states that immunological tolerance to a food depends on early exposure through the gastrointestinal tract whereas allergic sensitization is more likely, when foods expose the impaired skin barrier.[107] Among infants already sensitized to peanut before 6 months of age, high-dose exposure to peanut resulted in decreased rather than increased risk of peanut allergy.[104] This finding has been repeated with several other foods among children with high risk for allergies.[105] For tolerance induction, there may be a window open between 4 and 6 months of age.[108] In a prospective study, exposure to wheat before the age of 6 months reduced occurrence of allergy as compared with children who were given wheat first after 7 months of age.[109]

Early childhood oral tolerance induction is feasible in children who have not yet developed true food allergy for peanut or egg.[110] Oral immunotherapy is also a promising therapy for food allergy in older children up to adolescence. Efficacy has been shown in milk, peanut, egg, and wheat allergy. There is still debate about the proportion of patients reaching long-term immunological tolerance.[111] The immunological changes occurring during the OIT therapy are illustrated in Figure 7.

Atopic march is a cascade of atopic disease in childhood, generally with atopic eczema in early childhood predating other allergic disorders later in childhood. However, only approximately 7% of children with any atopic disease manifestation follow this path during childhood.[112]

Genetic factors have a major role in atopic disposition. For example, mutations in the gene coding for the protein filaggrin, linked to epidermal and mucosal homeostasis, predispose to eczema.[113] Children carrying the risk allele for mucosa-associated lymphoid tissue lymphoma translocation gene (MALT1) had the highest risk for peanut allergy.[114]

The outcome is derived much from the microbiome and environmental factors.[115] It is uncertain how much the microbial composition is affected primarily by the type 2 inflammatory response or is the immune deviation caused by a poorly developed microbiome? However, there is a clear association with both atopic eczema, food allergy and early life lung colonization with the microbiome.[116]

6 | CONCLUDING REMARKS

6.1 | Biodiversity sets limits to human existence

The terrestrial and aquatic ecosystems promote biomass production, stability, and pollination success, produce raw material for processing and manufacturing, support water circulation and freshwater resources, ensure food and support agriculture, sequestrate carbon from the atmosphere, prevent soil erosion, and provide a place for recreation. A long-term manipulative field experiment in Germany showed that about 45% of different types of ecosystem processes were affected by plant species richness.[117] However, the positive biodiversity effect seems to result from several mechanisms acting simultaneously, and functional diversity is even a stronger predictor of a healthy ecosystem than the structural one.[118] Loss of biodiversity reduces ecosystem productivity and stability.[119,120] Now, we are also increasingly aware of the adverse health effects of nature/biodiversity loss, allergic diseases, and asthma as examples.

Human kind has evolved from natural environments, that is from soil and natural waters, but is increasingly affected by built environment and urban space. The fuel for immunological resilience is exposure to biotically diverse life.[5] Human interaction with macro- and microdiversity is decisive.[121] Urban populations are short of natural experience, not only of exposure to micro-organisms but also to biogenic compounds.[122,123] The total exposure is also called the *exposome* that can help predict biological responses of the organism to the environment over time.[124]

Immunological resilience is dynamic and derived from exposure through life. The importance of diverse microbial exposure in early life to prevent allergy risk has been reported in both humans and mice.[125,126] Children, who live on farms, are exposed to a greater variety of environmental micro-organisms and have a lower prevalence of asthma and allergic disorders than children in reference groups.[10,37] In mouse models of allergic asthma, intranasal instillation of dust extracts from homes with high levels of endotoxins significantly inhibited airway hyperresponsiveness and eosinophilia.[37] Furthermore, exposure of mice to microbially rich and diverse soil modified composition of the intestinal microbiota, increased anti-inflammatory signaling in the intestinal epithelium, and protected against experimentally induced allergic asthma.[72] Skin and epithelial barrier has a constant crosstalk with the environment and dysfunctional barrier predisposes to various health risks.[127]

Resilience is central not only to individuals but to societies and populations by and large.[128,129] It is strengthened by an environment of multiple options giving room for choices. This is called *redundancy* in the biodiversity discussion. If one option fails, the other may succeed. In a biological or psychological monoculture, the failure of one may mean a failure of all. Biodiversity denotes abundance and even waste instead of extreme effectiveness. Paradoxically, waste creates buffers, that is, resilience. If a population is homogenous in the lack of immunity against COVID-19, it may face extinction. Unpredictable chaos is characteristic to nature. Order and efficacy are the dreams of man.

Prevention is always more cost-effective that medical treatment. World Allergy Organization published already in 2013 a position statement advocating a *Global Allergy Plan* to improve prevention and tolerance.[130] The Finnish nationwide, real-world intervention, controlled biodiversity interventions, and recent data on environmental epidemiology, microbiome, and epigenetics give credibility to the statement. Several initiatives for prevention are ongoing and new insights presented.[131-133] The next step should be systematic implementation studies. Digital transformation in health and care may speed up to obtain results.[134]

Avoidance of allergens causing severe symptoms will remain as good clinical practice but does not solve the public health problem. Probiotic bacteria protect somewhat against atopic eczema, but not generally against IgE-mediated allergies, respiratory outcomes in particular. There are still a number of unknown nutritional[135] and microbial factors that play a role in building immunological tolerance. For example, rhinovirus infections are associated with exacerbations of asthma. However, early rhinovirus infections as well as certain other enterovirus infections have associated with decreased risk of IgE-mediated sensitization.[136] In secondary (tertiary) prevention, allergen specific immunotherapy is effective, but not applicable at population level.

Along with allergy prevention, also measures for other chronic non-communicable diseases have been discussed for a good reason. For example, Nurminen and coworkers found recently that exposure to biodiverse agricultural environment in early life delays the onset of β-cell damaging process among genetically predisposed children and reduces the risk for type 1 diabetes.[137] Local communities and citizens need guidance to consider both human health and the environment.[138,139] The Finnish city of Lahti (120 000 inhabitants) is the Green Capital of European Union in 2021.[140] The city is preparing an educational 10-year plan to implement the best practices of public health and environmental care in the spirit of *Planetary Health*, which interconnects human health and the health of the planet.[141] The UN Agenda 2030 promotes individual-, community-, and system-level resilience for population well-being to reach the Sustainable Development Goals (SDGs).[142]

6.2 | Money talks

In 2011, the total value of global ecoservices was estimated $125–145 trillion. They contributed more than twice as much to human well-being than global gross domestic product (GDP).[143] Furthermore, more than half of the world's total GDP is fundamentally dependent on ecosystem services.[144] Their loss from 1997 to 2011 was worth of $4.3–20.2 trillion per year.[143] Only 0.19–0.25% of global GDP is yearly invested to sustain biodiversity.[145] This discrepancy makes no sense ecologically or economically. By protecting global biodiversity, we protect our health, general well-being, as well as our wallets.[146] Although the positive outcome of the Finnish allergy programme initiative was due to several factors, the cumulative, deferred savings of around €1,2 billion during the period from 2007 to 2018 tell of the potential of disease prevention in the health care.[147]

CONFLICT OF INTEREST

TH has received personal lecturing fees from GSK, Mundipharma, Orion Pharma, Sanofi, and MJM from GSK, Orion Pharma, outside of the submitted work. AS and HH are stakeholders and members of the board of Uute Scientific LtD which develops biodiversity-based interventions for the prevention of immune mediated diseases.

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